REMARKS

A. Status of the claims

Claims 70, 101, 132, 134, 163, 165 and 194 have been amended herein. Claims 1-69, 72-73, 79, 84, 103-104, 115, 135, 146, 166, 177, 196-197 and 208 have been canceled, thus claims 70-71, 74-78, 80-83, 85-102, 105-114, 116-134, 136-145, 147-165, 167-176, 178-195, 198-207 and 209-226 are currently pending.

Independent claims 70, 101, 132, 134, 163, 165 and 194 have been amended to incorporate the DNA contamination limitation of claim 1 of the case's parent application which issued as U.S. Patent 6,726,907 and which is set out below:

> 1. A purified adenovirus composition, the composition having a contaminating nucleic acid content of less than 400 pg per 10^{10} pfu virus and greater than or equal to about 60 pg per 10^{10} pfu virus.

Support for the indicated range can be found, for example in table 10 of the application which was described in detail in the Declaration of Joseph Senesac dated January 30, 2002 and which was made of record in U.S. Parent Application No. 09/556,570 (now U.S. Patent 6,726,907) to which the current application claims the benefit of priority.

B. Discussion of related cases

Applicants note that co-pending U.S. Patent Application No. 10/033,571 (the '571 case) is related to the instant application and both cases claim the benefit of priority to U.S. provisional patent application no. 60/031,329, filed on November 20, 1996. For example, the claims currently pending the '571 case concern:

> A method for making a purified adenovirus composition comprising:
>
> a) growing host cells in a media;
> b) providing nutrients to said host cells by perfusion or through a fed-batch process;
> c) infecting said host cells with an adenovirus;
> d) lysing said host cells to provide a cell lysate comprising adenovirus; and
> e) purifying adenovirus from said lysate by a process other than the use of cesium chloride density gradient centrifugation to provide a

pharmaceutically acceptable purified adenovirus composition having a contaminating nucleic acid content of less than 400 pg per 10^{10} pfu virus and greater than or equal to about 60 pg per 10^{10} pfu virus.

Pending claims in '571 case are currently under a 35 U.S.C. § 103 over Shabram (U.S. Patent 5,837,520), Huyghe *et al.* (Human Gene Therapy, 1995), Kozak *et al.* (Developments in Biological Standardization, 1996), Keay *et al.* (Biotechnology and Bioengineering, 1976), Nadeau *et al.* (Biotechnology and Bioengineering) and Griffiths (Animal Cell Biotechnology, 1986). The Examiner is invited to review the rejections set forth in this related case and a copy of the most recent Office Action in the '571 case has been submitted in the supplementary Information Disclosure Statement included herewith.

C. Declarations under 37 C.F.R. § 1.132

Included in the supplementary Information Disclosure Statement submitted herewith are two declarations under 37 C.F.R. § 1.132 of Drs. Peter Clarke and Shuyuan Zhang. These declarations were previously submitted to the USPTO in the connection with the prosecution of related U.S. Patent Application No. 10/033,571, discussed *supra*. In view of the related subject matter of these cases the declarations of Dr. Clarke and Dr. Zhang are believed to be relevant to the patentability of the currently pending claims and their entry into the record and consideration by the Examiner is respectfully requested.

D. Provisional Double Patenting Rejections

The Examiner has provisionally rejected claims 70-78 and 80-226 under the judicially created doctrine of obviousness type double patenting. However, at Applicants' request the provisional rejection has been held in abeyance until there is an indication fro the Examiner that claims are other wise allowable. Accordingly, Applicants do not further address the provisional rejection at this time.

E. The rejection under 35 U.S.C. § 112 should be withdrawn

The Examiner has maintained the new matter/lack of written description rejection of claims 78, 109, 140, 171 and 202 under 35 U.S.C. §112 (first paragraph), alleging

that the claim recitation that the therapeutic adenovirus composition is "essentially free of BSA" is not adequately described in the specification. Applicants traverse the rejection essentially for the reasons are already of record in the case.

The specification conveys with reasonable clarity to those skilled in the art that, as of the filling date sought, the inventors were in possession of the invention as now claimed. See Vac-Cath, Inc. v. Mahurkar,19 U.S.P.Q. 2d 1111 at 1117 (Fed. Cir. 1983). The Examiner's finding of "implicit support for such limitation" in the form of the method of Example 6 (*see, e.g.,* the August 8, 2006 Office Action at page 4, line 1-6) supports the language of their claim. The test for written description is whether the disclosure reasonable conveys to the worker of ordinary skill in the art that the inventors, at the time their application was filed, had possession of their claimed invention. An *ipsis verbis* disclosure is not necessary to satisfy the written description requirement. See In re Edwards, 196 U.S.P.Q. 465, 467 (CCPA 1978). Support for such claim language can be either implicit or explicit.

The skilled artisan reading the disclosure is instructed that one aspect of the invention is directed to the removal of contaminating proteins and viruses from the purified products of the invention. In particular, concerns over the outbreak of Bovine Spongiform Encephalopathy (BSE) ("mad cow disease") transmitted by infectious agents comprising abnormally structured bovine proteins (prions) dictates a particular concern with the removal of serum proteins. Thus, the specification teaches:

> "Historically, presence of bovine source proteins in cell culture media has been a regulatory concerns, especially recently because of the outbreak of Bovine Spongiform Encephalopathy (BSE) in some countries. Rigorous and complex downstream purification process has to be developed to remove contaminating proteins and any adventitious viruses from the final product. Development of serum-free 293 suspension culture is deemed to be a major process improvement for the production of adenoviral vector for gene therapy." (page 28, lines 11-17)

In order to accomplish this goal the specification teaches the adaptation of cells for growth in "serum-free" media .... "More particularly, the serum-free media comprises a fetal bovine serum content of less than 0.03% v/v." (page 7, lines 5-9) The resulting adenoviral product "should be **essentially free** of pyrogens, as well as other

impurities that could be harmful to humans or animals." (emphasis supplied, page 72, lines 15-17)

The specification also makes it clear to the reader that significant reduction in BSA content of the purified adenoviral product was a particularly important goal. For example, the specification states that "[a]s shown in FIG. 12, all the major adenovirus structure proteins are detected on the SDS-PAGE. The IEC purified virus shows equivalent staining as that of the double CsCl purified virus. Significant reduction in bovine serum albumin (BSA) concentration was achieved during purification. The BSA concentration in the purified virus was below the detection level of the western blot assay as shown in FIG. 13." Specification, page 92, , lines 4-8 [para. 0337]. And later, the specification notes that "[t]he purified virus was further analyzed by SDS-PAGE, western blot for BSA, and nucleic acid slot blot to determine the contaminating nucleic acid concentration. The analysis results are given in FIG. 19A, FIG. 19B and FIG. 19C, respectively." Page 96, lines 22-24 [para. 0352]. There can be no question but that reductions, and even removal entirely, of BSA was a principal goal of the inventors, a goal that was shown to have been achieved.

Taken together, these teachings that (1) bovine proteins constitute a significant and dangerous contaminant which should be removed from the therapeutic compositions; (2) the instruction that the compositions "should be essentially free of pyrogens, as well as other impurities..."; and (3) the demonstration that BSA could not be detected in the purified composition constitute an explicit disclosure that the Appellants were in possession of the invention of compositions "essentially free of BSA" as of their filing date.

For these reasons, the new matter/lack of written description rejection of dependent claims 78, 109, 140, 171 and 202 should be withdrawn.

F. The rejections under 35 U.S.C. § 103 should be withdrawn

In the Action the Examiner has reorganized the various claim rejections under 35 U.S.C. § 103 into groups I-IV. Applicants address each of the groups identified by the Examiner below.

I. Applicants traverse the rejection of claims 70-78 and 80-226 under 35 U.S.C. § 103(a) as allegedly obvious over Zhang et al., (U.S. Patent 6,410,010), further in view of Huyghe et al. (Human Gene Therapy, 1995), Perrin et al. (Vaccine, 1995) and Berg et al. (Biotechniques, 1993) for reasons that have been of record in the case. Nonetheless, in the interest expediting prosecution of the case, claims have been amended to further define the purity of viral compositions in the therapeutic methods as they related the amount of contaminating nucleic acid.

1. References cited by the examiner fail to teach all elements of the claims

The references cited in the instant rejection under 35 U.S.C. § 103 fail to teach all elements of the claims and thus there no *prima facie* for obviousness has been set forth. None of the references cited by the Examiner teach an adenoviral preparation that is having a contaminating nucleic acid content of less than 400 pg per 10^{10} pfu of virus and greater than or equal to about 60 pg per 10^{10} pfu of virus. The fact that these references provide no teaching regarding the level of nucleic acid contamination has been recognized by the Examiner. For example, the Examiner states that:

> As shown above, Zhang as evidenced by Huyghe and Perrin and optionally Berg, as optionally evidenced by Rowe make obvious the various aspects of claims 70, 101, 132, 163, and 194 in several manners as shown in Titles I-II, above; however, they do not specifically discuss obtaining nucleic acid contaminations less than 0.2ng/ml, and hence, the reader may argue that the Artisan would not have expected to obtain such levels of contamination. (August 23, 2007 Office Action at page 15)

Despite the fact that the cited references provide no teaching the regarding the level of nucleic acid contamination that can be achieved in adenoviral preparations, the Examiner appears to suggest that a low level of contaminating nucleic acid, such as that now recited in the claims is inherent in the teachings of Huyghe. Specifically, the Examiner argues that Huyghe teaches treating a lysate with nuclease (*i.e.*, Benzonase) to reduce nucleic acid contamination. Applicants disagree and note that the Patent Office has previously analyzed other references that discuss the use of Benzonase such as Shabram et al. (U.S. Patent 5,837,520) with respect to the level of nucleic acids contamination in adenoviral

preparations and found that they DO NOT teach the claimed low level of contamination. The Examiner is invited to review Applicants previous patent U.S. 6,726,907.

In the instant case, the Examiner has failed to provide sufficient evidence that Huyghe teaches adenoviral compositions having a level of nucleic acid contamination less than 0.2ng/ml and no evidence has been presented that the reference suggests that level than 400 pg per 10^{10} pfu of virus and greater than or equal to about 60 pg per 10^{10} pfu of virus could be achieved. Thus, the Examiner has failed to demonstrate that Huyghe inherently, or another other cited reference, teaches this element of the claims. The Federal Circuit has held that a proper rejection their must be supported by "substantial evidence" within the record, the Examiner has not met this burden. *In re Gartside,* 203 F.3d 1305, 1315 (Fed. Cir. 2000). In the case where a rejection relies upon the doctrine of inherency, inherency *may not* be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *In re Roberstson*, 169 F.3d 743, 745 (Fed. Cir 1999); *Continental Can Co. v. Monsanto Co.,* 948 F.2d 1264, 1269 (Fed. Cir. 1994). Furthermore any extrinsic evidence that is relied upon must "make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Telemac Cellular Corp. v. Topp Telecom, Inc.* 247 F3d 1316, 1328 (Fed. Cir. 2001); I*n re Roberstson,* 169 F.3d 743, 745 (Fed. Cir 1999); *Continental Can Co. v. Monsanto Co.,* 948 F.2d 1264, 1269 (Fed. Cir. 1994). It is clear that the current rejection has not met this burden with regarding to claims 74, 105, 136, 167 and 198 and hence the burden has not been met with regarding the currently amended claims.

The Examiner is referred to the declaration by Dr. Zhang that was submitted in the related '571 application and concerns the use of nucleases such as Benzonase to reduce the amount of contaminating nucleic acid in adenoviral preparations. As described by Dr. Zhang cell lysates contain high levels of contaminating nucleic acids. Huyghe teaches only treatment of crude cell lysate with benzonase, followed by further purification by Cesium Chloride gradient (see, page 1404, column 2, paragraph 2 of Huyghe). As stated by Dr. Zhang, benzonase has reduced activity when used in a crude cell lysate; for example, Dr Zhang indicates that the pH of a sample can significantly effect enzymatic activity. Thus, the skilled artisan would not expect the compositions of Huyghe to achieve a nucleic acid

contamination purity level that approaches the level of purity now recited in the claims. Thus, the references cited by the Examiner fail to demonstrate that the claimed level of purity would necessarily result from the methods of Huyghe and thus the Examiner has failed to support the rejection with the requisite "substantial evidence," formulate a *prima facie* case for obviousness.

Additionally, on page 9 of the instant Action the Examiner states that "[w]ith regarding to fed batch processes (e.g., Claim 83), Huyghe teaches feeding the batch (e.g., p. 1404, col. 1, paragraph 5)." However, Applicants note that while Huyghe teaches infecting cells in a culture Huyghe does not teach providing nutrients to cells through a fed-batch process. Thus, the Examiner has failed to identify any art of record that teaches this aspect of the claimed methods.

II. Applicants traverse the rejection of claims 70-78, 80-90, 96-121, 127-152, 158-183, 189-214 and 220-226 under 35 U.S.C. § 103(a) as allegedly obvious over Zhang et al., further in view of Huyghe et al., and Perrin et al. as further evidenced by Rowe et al. (*J. Viol*, 1981). In this further rejection the Examiner cites Rowe et al. as teaching that adenoviruses are capable of growth in BHK-21 cells. Rowe et al. does not, however, remedy the failure of Zhang et al., Huyghe et al., and Perrin et al. to disclose or suggest a recited purity level of the adenoviral composition as now recited in the claims. Accordingly, the combination of Zhang et al., Huyghe et al., Perrin et al. and Rowe et al. fails to disclose or suggest the subject matter of any of the rejected claims and no *prima facie* basis for rejecting claims under 35 U.S.C. § 103(a) has been established.

III. Applicants traverse the rejection of claims 101-109, 111-140, 142-171, 173-202 and 204-226 under 35 U.S.C. 103(a) as allegedly obvious over Zhang et al., further in view of Huyghe et al., and Perrin et al. However, as detailed *supra*, none of these references either alone or in combination teach or suggest the claim recited level of purity of the adenoviral composition.

IV. Applicants traverse the rejection of claims 74, 105, 136, 167 and 198 under 35 U.S.C. 103(a) as allegedly obvious over Zhang et al., further in view of Huyghe et al., Perrin et al., optionally in view of, Berg et al. and/or Rowe et al. and further in view of

further in view of Nadeau et al., or Trepanier et al. Specifically, in the additional rejection, the Examiner addresses claims which recite limitations related to the purity of virus vis-à-vis the concentration of contaminating nucleic acid per unit volume (*i.e.*, preparations having a contaminating nucleic acid level 0.2ng/ml or less). The Examiner argues that Nadeau et al. and Trepanier et al. each "teach the use of ultrafiltration in the purification of viral particles," (August 23, 2007 Office Action at page 15). However, neither Nadeau et al. nor Trepanier et al. remedy the failure of Zhang et al., Huyghe et al., Perrin et al., Berg et al. and Rowe et al. to teach or suggest the claim recited level of purity of the adenoviral composition.

First of all, the Examiner erroneously cites page 615, column 1, paragraph 1 of Nadeau et al. as teaching purification of adenovirus using ultrafiltration. As summarized by Dr. Clarke in his declaration that was submitted in the related '571 case on October 31, 2007 (submitted in the information disclosure statement filed herewith). Nadeau et al. concerns methods for purifying proteins and not methods for purifying adenoviruses; see for example paragraph 3 of the declaration which notes that "the data shown in Nadeau are exclusively restricted to the production of recombinant proteins." Accordingly, the passage of Nadeau et al. cited in the rejection teaches that "Viral particles were **removed** by filtration through Ultrafree-MC (millpore, Bedford, MA) filters," emphasis added, (page 615, column 1, paragraph 1). Thus, Nadeau et al. provides no teaching or suggestion that is relevant to purification or methods of treatment with adenoviruses.

Likewise, Trepanier et al. does not provide any teaching regarding adenoviral purification. First of all, the passage in Trepanier et al. cited by the examiner on page 203, column 2, second paragraph of Trepanier et al. describe ultrafiltration of respiratory syncytial virus (RSV) wherein the ultrafiltration was "used to for virus concentration." Thus, Trepanier et al. does not provided any teaching regarding the use of ultrafiltration to purify viruses, much less to reduce nucleic acid contamination. Furthermore, Trepanier et al. provides no teaching regarding purification or treatment methods with adenovirus; rather Trepanier et al. concerns completely unrelated RSV particles. As evidence of the many differences between RSV (a paramyxovirus) and adenovirus, the Examiner is referred to paragraphs 11 and 12 of the declaration of Dr. Shuyuan Zhang that was made of record in the instant case along with a response to Office Action filed on February 27, 2006. In the declaration Dr. Zhang discuses the differences in the physical properties of paramyxoviruses

as compared to adenoviruses. Thus, Applicants assert that Trepanier et al. is not relevant to the instant rejection because it provides no teaching regarding the claim recited level of nucleic acid purity and provides no teaching regarding purification of adenovirus by ultrafiltration or by any other method.

Finally, the Examiner states that "Applicant's specification makes clear that such [an] ultrafiltration step yields the desired levels of contaminating nucleic acids" and cites Table 10 of the specification at page 93. However, Table 10 assess nucleic acid contamination in adenoviral preparations at various steps in purification and shows that **concentration** of the virus by ultrafiltration results in only meager reductions in the level nucleic acid contamination in preparations. Thus, contrary to the Examiner's argument, Table 10 provides evidence that ultrafiltration of adenovirus would not result in the claimed low levels of nucleic acid contamination.

Thus, as discussed *supra*, no *prima facie* rejection of the pending claims under 35 U.S.C. 103 over Zhang et al., Huyghe et al., Perrin et al., Berg et al. and Rowe et al. has been set forth and neither Nadeau et al., nor Trepanier et al. remedy this failure. Accordingly, removal of the rejection is requested.

G. Conclusion

In view of the above amendment and argument, Applicants believes the pending application is in condition for allowance and such favorable action is requested. The Examiner is invited to contact the undersigned to discuss the case.

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